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Strategy for the Synthesis of Pyrazolo[5,1-*d*][1,2,5]triazepinones, a New Heterocyclic System

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Abstract—A preparative procedure has been developed for the synthesis of 4-oxo-7-phenyl-5,8-dihydro-4*H*-pyrazolo[5,1-*d*][1,2,5]triazepine-2-carbohydrazide, the first representative of a new heterocyclic system, by recyclization of methyl 4-oxo-6-phenyl-4*H*-pyrazolo[5,1-*c*][1,4]oxazine-2-carboxylate with hydrazine hydrate.

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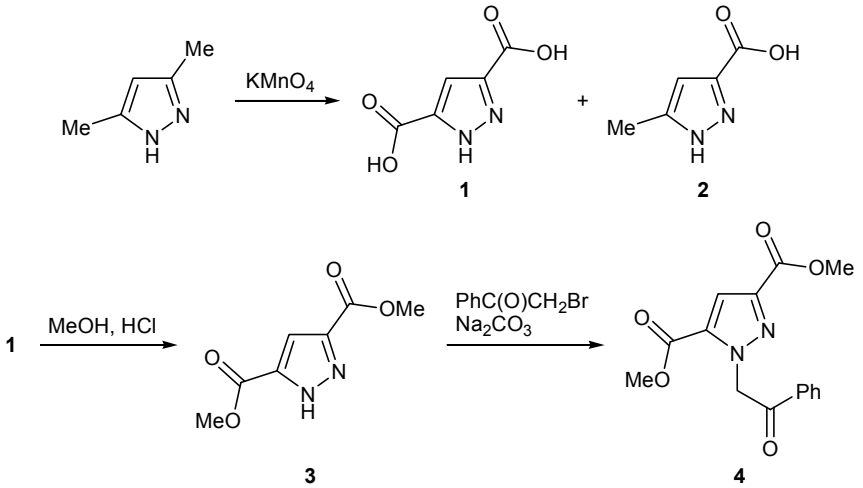
Seven-membered nitrogen heterocycles and their hetero-fused derivatives are structural fragments of many biologically active compounds and modern medicinal agents. Among these, 1,4- and 2,3-benzodiazepines are very important. Drugs based thereon are used for the treatment of anxieties, epilepsy, malignant glioma, lateral amyotrophic sclerosis, and Parkinson's and Alzheimer's diseases; they exhibit anticonvulsant activity and may be used as minor tranquilizers [1–6]. Benzotriazepines and benzotriazepinones possess various biological activities; in particular, they act as antagonists of cholecystokinin receptor (CCK2) and parathyroid peptide-related hormone receptor (PTH1R); psychotropic compounds of these series are characterized by a lower number of side effects than benzodiazepine derivatives [6, 7].

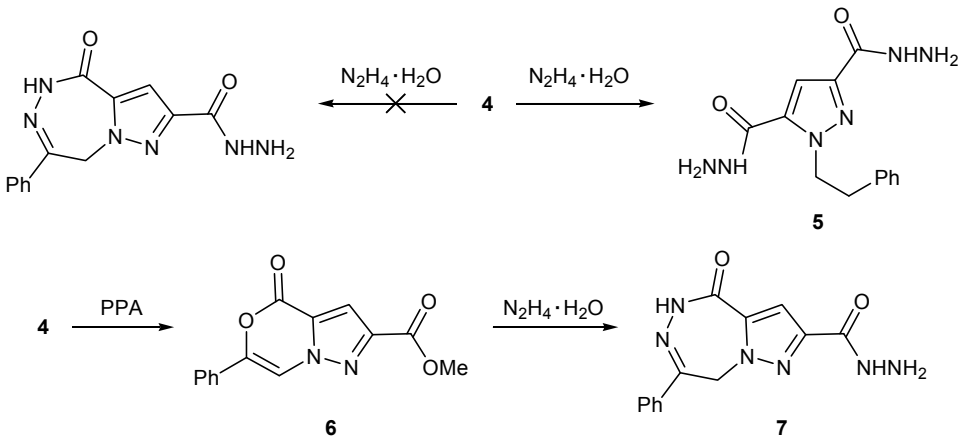
Hetero-fused 1,2,5-triazepines with a bridgehead nitrogen atom can be used as neurotropic agents [7]. Pyrazolo[1,2-*a*][1,2,5]triazepine derivatives affect central nervous system [8] and exhibit pesticidal and herbicidal activities [7]. However, such compounds remain so far difficultly accessible because of the lack of a general method of their synthesis.

While initiating studies on the synthesis of pyrazolo[5,1-*d*][1,2,5]triazepines from accessible reagents, I have found no published data on this fused heterocyclic system. The strategy for building up pyrazolo[5,1-*d*][1,2,5]triazepine skeleton was developed on the basis of known methodology for diazepine ring fusion to benzene ring or other heterocycle. 2,3-Benzodiazepinones and their heterocyclic analogs were successfully synthesized previously by reactions of 1,5-di-

Scheme 1.



Scheme 2.



ketones or 2-aroyl(acetyl)phenylacetic acids and their esters with hydrazine [9–11]. Therefore, dimethyl 1-(2-oxo-2-phenylethyl)-1*H*-pyrazole-3,5-dicarboxylate (**4**) was selected as probable precursor to pyrazolo[5,1-*d*]-[1,2,5]triazepine.

The oxidation of 3,5-dimethylpyrazole with potassium permanganate gave a mixture of 1*H*-pyrazol-3,5-dicarboxylic acid (**1**) [12] and 5-methyl-1*H*-pyrazole-3-carboxylic acid (**2**) (Scheme 1). Acids **1** and **2** were separated by precipitation from aqueous solution at different pH values. Esterification of **1** with methanol, followed by alkylation of dimethyl 1*H*-pyrazole-3,5-dicarboxylate (**3**) with phenacyl bromide afforded dimethyl 1-(2-oxo-2-phenylethyl)-1*H*-pyrazole-3,5-dicarboxylate (**4**).

It was expected that heating of **4** in hydrazine hydrate would give rise to 4-oxo-7-phenyl-5,8-dihydro-4*H*-pyrazolo[5,1-*d*][1,2,5]triazepine-2-carbohydrazide. However, the only isolated product was 1-(2-phenylethyl)-1*H*-pyrazole-3,5-dicarbohydrazide (**5**, yield 10%; Scheme 2). Further accumulation of compound **5** was observed when the filtrate obtained after separation of **5** was heated under reflux. Obviously, the Wolff–Kishner reduction of the ketone carbonyl group in **4** occurred under milder conditions than those typical of such reactions. Heating of **4** in polyphosphoric acid (PPA) led to the formation of methyl 4-oxo-6-phenyl-4*H*-pyrazolo[5,1-*c*][1,4]oxazine-2-carboxylate (**6**) (Scheme 2).

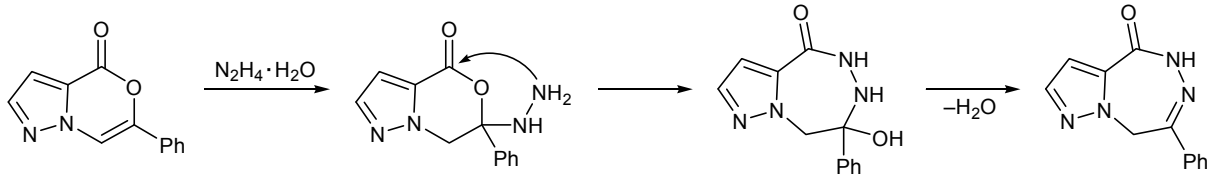
2,5-Dihydro-5*H*-2,3-benzodiazepin-1-one [13] and pyrrolo[3,4-*d*][1,2]diazepinone derivatives [9] were synthesized previously in preparative yields by reactions of 3-(3,4-dimethoxyphenyl)-1*H*-isochromen-1-one and pyrano[3,4-*c*]pyrrol-4(2*H*)-one with hydrazine hydrate. Taking these results into account, compound **6** was used as starting material for the synthesis of pyrazole fused to triazepine. In fact, pyrazolooxazine **6** reacted with hydrazine hydrate in isopropyl alcohol under reflux to give 57% of 4-oxo-7-phenyl-5,8-dihydro-4*H*-pyrazolo[5,1-*d*][1,2,5]triazepine-2-carbohydrazide (**7**) (Scheme 2). A probable reaction mechanism is shown in Scheme 3. The triazepinone ring is formed via expansion of the lactone ring (without opening) with hydrazine, followed by elimination of water molecule.

Taking into account accessibility of the initial reactants and good yield, the proposed procedure for the synthesis of 4-oxo-7-phenyl-5,8-dihydro-4*H*-pyrazolo[5,1-*d*][1,2,5]triazepine-2-carbohydrazide by reaction of methyl 4-oxo-6-phenyl-4*H*-pyrazolo[5,1-*c*]-[1,4]oxazine-2-carboxylate with hydrazine hydrate may be recommended for preparative purposes.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer at 400 and 100 MHz, respectively, using DMSO-d_6 as solvent and tetra-

Scheme 3.



methylsilane as internal standard. The IR spectra were measured in KBr on a Specord IR-75 instrument. The melting points were determined on a Boetius hot stage and are uncorrected.

1*H*-Pyrazole-3,5-dicarboxylic acid (1). 3,5-Dimethyl-1*H*-pyrazole, 78.5 g (0.818 mol), was dissolved in 700 mL of water heated to 70°C, and 517 g (3.271 mol) of potassium permanganate was added to the hot solution, maintaining the temperature no higher than 90°C. The mixture was cooled to room temperature, the precipitate of MnO_2 was filtered off and washed with water, and the filtrate was acidified with aqueous HCl to pH 2 and left overnight. The precipitate was filtered off and washed with water. Yield 41.75 g (33%), white crystals, mp 257–258°C. ^{1}H NMR spectrum: δ 7.07 ppm, s (1H, 4-H).

5-Methyl-1*H*-pyrazole-3-carboxylic acid (2). The aqueous filtrate obtained after separation of diacid **1**, was neutralized to pH 5–6, and the precipitate of **2** was filtered off and washed with water. Yield 18.1 g (18%), white crystals, mp 210–211°C. ^{1}H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 6.42 s (1H, 4-H).

Dimethyl 1*H*-pyrazole-3,5-dicarboxylate (3). A mixture of 31.7 g (0.203 mol) of diacid **1** and 125 mL of methanol was saturated with gaseous HCl. The mixture was refluxed for 3 h and left overnight at room temperature. The precipitate was filtered off and washed with methanol. Yield 23.5 g (63%), white crystals, mp 142–143°C. IR spectrum, ν, cm^{-1}: 3105 br (NH), 1710 s (C=O), 1240 s (C–O–C). ^{1}H NMR spectrum, δ, ppm: 3.82 s (6H, CH_3), 6.36 s (1H, 4-H), 14.43 s (1H, NH).

Dimethyl 1-(2-oxo-2-phenylethyl)-1*H*-pyrazole-3,5-dicarboxylate (4). A mixture of 20.4 g (0.111 mol) of diester **3**, 33.19 g (0.167 mol) of phenacyl bromide, and 23.5 g (0.222 mol) of sodium carbonate in 100 mL of DMF was stirred for 13 h at 85°C. The mixture was poured into water, and the precipitate was filtered off and recrystallized from methanol. Yield 15.6 g (47%), colorless crystals, mp 127–128°C. IR spectrum, ν, cm^{-1}: 1695 s (C=O), 1220 s (C–O–C). ^{1}H NMR spectrum, δ, ppm: 3.81 s (3H, CH_3), 3.87 s (3H, CH_3), 6.17 s (2H, CH_2), 7.31 s (1H, CH), 7.56 t (2H, CH, *J* = 7.6 Hz), 7.67 t (1H, CH, *J* = 7.2 Hz), 8.05 d (2H, CH, *J* = 7.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 50.27 (CH_3), 50.78 (CH_3), 57.90 (CH_2), 111.66, 126.65, 127.39, 132.47, 132.51, 132.77, 140.37, 157.47 (C=O), 159.62 (C=O), 190.33 (C=O). Found, %: C 59.53; H 4.73; N 9.22. $C_{15}H_{14}N_2O_5$. Calculated, %: C 59.60; H 4.67; N 9.27.

1-(2-Phenylethyl)-1*H*-pyrazole-3,5-dicarbohydrazide (5). A mixture of 1 g (3.70 mmol) of **4** and 7 mL of hydrazine hydrate was refluxed for 2 h. Excess hydrazine hydrate was evaporated by half, and the residue was left to stand overnight at room temperature. The precipitate was filtered off and washed with water. Yield 0.1 g (10%), white crystals, mp 220–221°C. IR spectrum, ν, cm^{-1}: 3700 br (NH), 3240 br (NH_2), 1660 s (C=O), 1620 s (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 3.09 t (2H, CH_2, *J* = 7.6 Hz), 4.38 br.s (4H, NH_2, *J* = 7.6 Hz), 4.74 t (2H, CH_2, *J* = 7.6 Hz), 7.28–7.17 m (6H, CH), 9.06 s (1H, NH), 9.83 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 38.5 (CH_2), 54.5 (CH_2), 109.2, 128.3, 130.2, 130.6, 137.0, 139.8, 145.7, 160.4 (C=O), 162.4 (C=O). Found, %: C 54.21; H 5.67; N 29.23. $C_{13}H_{16}N_6O_2$. Calculated, %: C 54.16; H 5.59; N 29.15.

Methyl 4-oxo-6-phenyl-4*H*-pyrazolo[5,1-*c*][1,4]-oxazine-2-carboxylate (6). A mixture of 1 g (3.31 mmol) of **4** and 6 g of polyphosphoric acid was heated for 1 h at 140°C. The mixture was diluted with excess methanol, and the precipitate was filtered off. Yield 0.35 g (39%), white crystals, mp 197–198°C. IR spectrum, ν, cm^{-1}: 1750 s (C=O), 1695 s (C=C_{arom}), 1250 s (C–O–C). ^{1}H NMR spectrum, δ, ppm: 3.91 s (3H, CH_3), 7.47–7.59 m (4H, H_{arom}), 7.87 d (2H, CH, *J* = 6.8 Hz), 8.79 s (1H, CH). ^{13}C NMR spectrum, δ_C, ppm: 50.98 (CH_3), 106.21, 109.18, 123.28, 126.75, 127.72, 128.01, 128.86, 142.50, 142.83, 151.67 (C=O), 159.55 (C=O). Found, %: C 62.19; H 3.80; N 10.41. $C_{14}H_{10}N_2O_4$. Calculated, %: C 62.22; H 3.73; N 10.37.

4-Oxo-7-phenyl-5,6-dihydro-4*H*-pyrazolo[5,1-*d*]-[1,2,5]triazepine-2-carbohydrazide (7). A mixture of 0.5 g (1.85 mmol) of **6** and 0.37 g (7.41 mmol) of hydrazine hydrate in 5 mL of isopropyl alcohol was refluxed for 3 h. The solution was cooled to room temperature, and the precipitate was filtered off. Yield 0.3 g (57%), white crystals, mp 186–187°C. IR spectrum, ν, cm^{-1}: 3300 br (NH), 1680 s (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 5.73 s (2H, CH_2), 7.08–7.26 m (6H, CH), 7.68 d (2H, CH, *J* = 6.4 Hz), 9.25 s (1H, NH), 10.04 s (1H, NH. ^{13}C NMR spectrum, δ_C, ppm: 46.31 (CH_2), 108.90, 127.23, 129.10, 130.04, 137.82, 139.84, 141.51, 146.28, 160.74 (C=O), 162.18 (C=O). Found, %: C 54.87; H 4.29; N 29.55. $C_{13}H_{12}N_6O_2$. Calculated, %: C 54.93; H 4.25; N 29.56.

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